Of mice and men: asymmetric interactions between *Bordetella* pathogen species

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SUMMARY

In a recent experiment, we found that mice previously infected with *Bordetella pertussis* were not protected against a later infection with *Bordetella parapertussis*, while primary infection with *B. parapertussis* conferred cross-protection. This challenges the common assumption made in most mathematical models for pathogenic strain dynamics that cross-immunity between strains is symmetric. Here we investigate the potential consequences of this pattern on the circulation of the two pathogens in human populations. To match the empirical dominance of *B. pertussis*, we made the additional assumption that *B. parapertussis* pays a cost in terms of reduced fitness. We begin by exploring the range of parameter values that allow the coexistence of the two pathogens, with or without vaccination. We then track the dynamics of the system following the introduction of anti-pertussis vaccination. Our results suggest that (1) in order for *B. pertussis* to be more prevalent than *B. parapertussis*, the former must have a strong competitive advantage, possibly in the form of higher infectivity, and (2) because of asymmetric cross-immunity, the introduction of anti-pertussis vaccination should have little effect on the absolute prevalence of *B. parapertussis*. We discuss the evidence supporting these predictions, and the potential relevance of this model for other pathogens.

Key words: whooping cough, mathematical model, strain dynamics, vaccine.

INTRODUCTION

Understanding how pathogen diversity and evolution interact with epidemiology is crucial to improve the control of infectious diseases. Multi-disciplinary approaches, combining microbiology and genetics with mathematical and statistical modelling, have allowed rapid progress in this field over the last decade (Grenfell *et al*. 2004). A key objective is to determine in what measure the (re-) emergence of a disease (whether it has already occurred or it is anticipated) is caused by changes in the host population or by evolution of the pathogen. Antimicrobial resistance and antigenic variation are certainly two of the most serious threats to sustained control of infectious diseases. Here we will focus on the latter. Antigenic diversity enables infectious agents to evade host's acquired immunity. It can occur within a single host, allowing the infection to persist (see review by Frank and Barbour, 2006), or at the population level, causing recurrent epidemics such as seen in human influenza (Gog and Grenfell, 2002; Ferguson, Galvani and Bush, 2003; Koelle *et al*. 2006), cholera (Koelle *et al*. 2006) or dengue (Wearing and Rohani, 2006). In all those examples, mathematical models have been used to decipher the role of ecological and evolutionary dynamics, based on experimental and epidemiological data.

In this paper we demonstrate how a simple model can be derived and analysed to explore the potential implications at the population level of experimental findings at the individual level. The starting point is a recent experimental study (Wolfe *et al*. 2007) that showed asymmetric cross-immunity between two closely-related bacterial species: *Bordetella pertussis* and *B. parapertussis*. These two pathogens are the main agents of whooping cough (Mattoo and Cherry, 2005) and are specific to humans. However, infections of mice have proven a useful assay to study pathology (Sato *et al*. 1980), immunity (Sato and Sato, 1984) and vaccine protection (Redhead *et al*.

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1993; Willems *et al*. 1998). The relationship between *B. pertussis* and *B. parapertussis* has been debated since the latter was isolated in 1937 (Eldering and Kendrick, 1938, 1952; Granström and Askelöf, 1982). Clinically, *B. parapertussis* produces similar but typically milder symptoms than *B. pertussis* (Lautrop, 1958; Mastrantonio *et al*. 1998; Bergfors *et al*. 1999; He *et al*. 1999; Liese *et al*. 2003). Genetically, the two human pathogens now appear to have emerged independently from different animal strains of *B. bronchiseptica* (Diavatopoulos *et al*. 2005). More controversial is the level of cross-protective immunity conferred by *B. pertussis* and *B. parapertussis*. Lautrop (1958) reported 73 children who became infected with both *B. pertussis* and *B. parapertussis* over a 17-year period, and concluded that ''preventive cross-immunity [...] does not exist''. Khelef *et al*. (1993) showed that purified proteins from either *B. pertussis* or *B. parapertussis* do not provide mice with cross-protection in aerosol challenge experiments. This lack of cross-protection was supported by several studies from clinical trials that suggested poor efficacies of anti-pertussis vaccines against *B. parapertussis* (Mastrantonio *et al*. 1998; Stehr *et al*. 1998; Bergfors *et al*. 1999). In contrast, Watanabe and Nagai (2001) found that mice previously infected with either of the two pathogens were able to clear both pathogens when challenged six weeks later. However, the use of *B. pertussis* strain 18-323, which presents a number of striking molecular differences with other *B. pertussis* strains (Musser *et al*. 1986; Stibitz and Yang, 1997; Diavatopoulos *et al*. 2005), and the long delay (two weeks) before assessing clearance of infection, is a cause of concern regarding the relevance of the latter result. Using previously sequenced strains of *B. pertussis* and *B. parapertussis*, we recently performed challenge experiments in mice four weeks after the initial infection (Wolfe *et al*. 2007). Bacterial counts three days post-challenge show that, compared to naïve mice, those immunised with *B. pertussis* were able to clear subsequent infection with *B. pertussis* but not *B. parapertussis*. Conversely, immunization with *B. parapertussis* elicited the clearance of both species. We then established, experimentally, the key role of O-antigen (which *B. pertussis* lacks) in enabling *B. parapertussis* to evade cross-immunity: in a similar experiment, an O-antigen-deficient *B. parapertussis* strain showed reduced ability to colonise hosts previously challenged with either species (Wolfe *et al*. 2007).

These experimental results from the mouse model system suggest that *B. parapertussis* may have a competitive advantage over *B. pertussis* in human populations. By contrast, the observed incidence of *B. parapertussis* has consistently been lower than that of *B. pertussis* (Lautrop, 1971; He *et al*. 1998; Mastrantonio *et al*. 1998; Bergfors *et al*. 1999; Cimolai and Trombley, 2001; Frühwirth *et al*. 2002; Liese *et al*. 2003; Dragsted *et al*. 2004; Letowska and Hryniewicz, 2004). However, most of these surveys are likely to underestimate the circulation of *B. parapertussis* as it tends to cause milder symptoms – and therefore is more likely to go unreported – than *B. pertussis*. In addition, in some countries like the United States, *B. pertussis* infections are notifiable while *B. parapertussis* infections are not (Centers for Disease Control and Prevention, 2007). Lautrop (1971), who produced the most detailed epidemiological study of *B. parapertussis* available, went so far as to assert that ''as an infectious entity parapertussis is as widespread as pertussis.'' Besides, there have been no recent longitudinal studies that could show trends in *B. parapertussis* circulation. In view of the shortcomings of current epidemiological data, we designed a mathematical model to investigate the potential effects of asymmetric cross-immunity on the coexistence, incidence and dynamics of *B. pertussis* and *B. parapertussis* within a human population. Although many aspects of pathogen strain dynamics have already been modelled, asymmetric cross-immunity has been widely overlooked. To our knowledge the only two exceptions are studies by White, Cox and Medley (1998) who considered the possibility from a theoretical point of view, and Lipsitch *et al*. (2000) who measured experimentally and modelled mathematically asymmetric cross-immunity among strains of *Streptococcus pneumoniae*. This paper will address the following questions. Assuming asymmetrical cross-immunity and fitness difference, what conditions allow the coexistence of the two pathogens? How do the parameters of the model affect their prevalence? How does the introduction of anti-pertussis vaccination affect the dynamics of the two species? Beyond the particular case of *B. pertussis* and *B. parapertussis*, we suspect that careful experimental studies could reveal similar patterns in other systems, so that our model could be applied more broadly.

METHODS

The model

Our model is an extension of the classical SIR framework (for Susceptible-Infectious-Recovered) to two pathogenic entities, similar to that used by Kamo and Sasaki (2002) with the addition of a vaccinated compartment. As shown in Fig. 1, the host population falls into 10 non-overlapping compartments, defined by their levels of infectivity and susceptibility with respect to the two pathogens. Their dynamics are described by the following system of

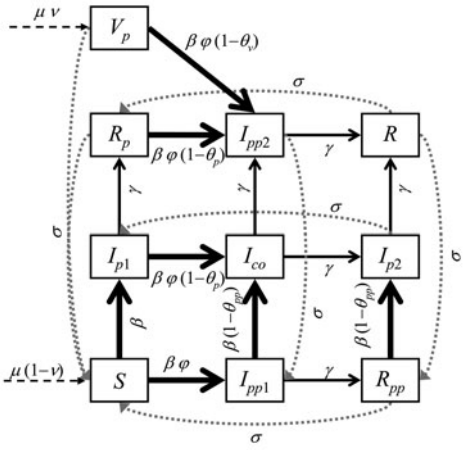

Fig. 1. Diagram of the dynamic model described by equations (1). Boxes represent the ten compartments into which the population is divided, and arrows show transfers of individuals between them. Solid thick arrows: infections; solid thin arrows: recoveries; dotted grey arrows: loss of immunity; dashed arrows: births. Deaths (occurring at equal rates in all compartments) are not shown.

ordinary differential equations:

$$\begin{cases} dS/dt = \mu(1-v-S) - S(\Lambda_p + \Lambda_{pp}) + \sigma(R_p + R_{pp} + V_p) \\ dV_P/dt = \mu(v - V_p) - (1-\theta_v)V_p\Lambda_{pp} - \sigma V_p \\ dI_{p1}/dt = S\Lambda_p - (\mu+\gamma)I_{p1} - (1-\theta_p)I_{p1}\Lambda_{pp} + \sigma I_{p2} \\ dI_{pp1}/dt = S\Lambda_{pp} - (\mu+\gamma)I_{pp1} - (1-\theta_{pp})I_{pp1}\Lambda_p + \sigma I_{pp2} \\ dI_{co}/dt = (1-\theta_{pp})I_{pp1}\Lambda_p + (1-\theta_p)I_{p1}\Lambda_{pp} - (\mu+2\gamma)I_{co} \\ dR_p/dt = \gamma I_{p1} - (\mu+\sigma)R_p - (1-\theta_p)R_p\Lambda_{pp} + \sigma R \\ dR_{pp}/dt = \gamma I_{pp1} - (\mu+\sigma)R_{pp} - (1-\theta_{pp})R_{pp}\Lambda_p + \sigma R \\ dI_{p2}/dt = (1-\theta_{pp})R_{pp}\Lambda_p + \gamma I_{co} - (\mu+\gamma+\sigma)I_{p2} \\ dI_{pp2}/dt = (1-\theta_p)R_p\Lambda_{pp} + (1-\theta_v)V_p\Lambda_{pp} + \gamma I_{co} - (\mu+\gamma+\sigma)I_{pp2} \\ dR/dt = \gamma(I_{p2} + I_{pp2}) - (\mu+2\sigma)R \end{cases} \quad (1)$$

Table 1 defines the symbols used in the model. In line with empirical observations (e.g. Lautrop, 1971), we allow for the possibility of co-infection by the two pathogens. We make the following assumptions about immunity: upon infection with one pathogen, individuals are fully protected against re-infection with the same pathogen, but only partially protected against secondary infection with the other pathogen. Similarly, vaccination of newborns protects them against infection with *B. pertussis* and reduces their susceptibility to *B. parapertussis*. All immunity wanes at a constant rate σ, i.e. individuals lose their immunity against that pathogen on average $1/\sigma$ years after recovering from an infection (or after vaccination). To our knowledge there is no empirical indication on how measures of bacterial growth in challenge experiments, as performed by Wolfe *et al.* (2007), can be used to quantify variations in susceptibility or infectiousness in an epidemiological context. We decided to represent partial cross-immunity by a reduction in susceptibility to secondary infection, represented by parameters θ_p, the level of cross-protection conferred by infection with *B. pertussis*, and θ_{pp}, that conferred by infection with *B. parapertussis*. To account for asymmetric cross-immunity, we impose the following inequalities: $0 \leqslant \theta_p < \theta_{pp} \leqslant 1$. We found no empirical indication on the level of cross-protection (against *B. parapertussis*) conferred by anti-pertussis vaccination, θ_v, compared to cross-protection from infection with *B. pertussis*, θ_p. By default, we assume that the two parameters are equal, but we also consider other possibilities.

In addition, to account for the alleged lower incidence of *B. parapertussis*, we allow for the possibility of a fitness cost which would balance its immunity-based competitive advantage. Compared to the baseline transmission rate β of *B. pertussis*, we therefore assume that the transmission rate of *B. parapertussis* is $\beta\varphi$, with $0 < \varphi \leqslant 1$. Alternatively, we considered an increase in the recovery rate of *B. parapertussis*, γ/φ, which led to very similar results, so we will not present this scenario here. Although we are not aware of any direct evidence of such a fitness difference between *B. pertussis* and *B. parapertussis*, the fact that the latter tends to exhibit milder or shorter symptoms could account for lower or shorter-lived infectivity. The previous assumptions are summarised in Table 2, which shows the infection rates of the two pathogens on the different classes of susceptible hosts. We wish to emphasize that these assumptions represent one possible interpretation of the implications of experimental observations at the individual level for population dynamics.

Analyses

Due to the high dimensionality of the system, little algebraic analysis is feasible, so we resorted mainly to numerical analysis. First, we studied single pathogen

Table 1. List of symbols used in the model

S	Proportion of fully susceptible individuals
V	Proportion of uninfected vaccinated individuals
I_{p1}	Proportion of primary infections with *B. pertussis*
I_{pp1}	Proportion of primary infections with *B. parapertussis*
I_{co}	Proportion of co-infections
R_p	Proportion of individuals immune to *B. pertussis* after primary infection
R_{pp}	Proportion of individuals immune to *B. parapertussis* after primary infection
I_{p2}	Proportion of secondary infections with *B. pertussis*
I_{pp2}	Proportion of secondary infections with *B. parapertussis*
R	Proportion of individuals immune to both pathogens after secondary infection
β	Transmission rate of *B. pertussis*
$\beta\varphi$	Transmission rate of *B. parapertussis*
Λ_p	Force of infection of *B. pertussis*: $\Lambda_p=\beta(I_{p1}+I_{p2}+I_{co})$
Λ_{pp}	Force of infection of *B. parapertussis*: $\Lambda_{pp}=\beta\varphi(I_{pp1}+I_{pp2}+I_{co})$
μ	Natural birth and death rate
v	Vaccine coverage: proportion of newborns who receive the anti-pertussis vaccine
σ	Rate of loss of immunity
θ_p	Protection conferred by primary infection with *B. pertussis* against *B. parapertussis*
θ_{pp}	Protection conferred by primary infection with *B. parapertussis* against *B. pertussis*
θ_v	Protection conferred by anti-pertussis vaccination against *B. parapertussis*
γ	Rate of recovery
R_0	Basic reproduction number of *B. pertussis*

Table 2. Per capita forces of infection for the different categories of susceptible hosts by *B. pertussis* and *B. parapertussis*

Category	*B. pertussis*	*B. parapertussis*
S	$\beta(I_{p1}+I_{p2}+I_{co})$	$\beta\varphi(I_{pp1}+I_{pp2}+I_{co})$
V	0	$\beta\varphi(1-\theta_v)(I_{pp1}+I_{pp2}+I_{co})$
I_{p1}, R_p	0	$\beta\varphi(1-\theta_p)(I_{pp1}+I_{pp2}+I_{co})$
I_{pp1}, R_p	$\beta(1-\theta_{pp})(I_{p1}+I_{p2}+I_{co})$	0

equilibrium states to derive criteria for the persistence of *B. pertussis* and *B. parapertussis*. We then investigated the relative incidence of the two pathogens and certain aspects of their endemic dynamics. Analyses were carried out with Mathematica 6.0 (Wolfram, 2007).

We chose the numerical values of certain parameters based on the limited available information from clinical studies and previous modelling works. The average infectious period for both pathogens, $1/\gamma$, was set to 21 days (Anderson and May, 1982). Published data suggests that loss of immunity appears within 6 to 10 years of primary infection or vaccination (Olin *et al.* 2003; Broutin *et al.* 2004), although there is no indication on the distribution of the duration of immunity in populations. Following Wearing and Rohani (unpublished manuscript), we set the average duration of immunity $1/\sigma$ to 50 years, which enabled them to successfully reproduce the dynamical features of *B. pertussis* incidence in England and Wales. Note that, because loss of immunity in our model is assumed to be exponentially-distributed, this value amounts to nearly 10% of people losing their immunity within a five year period. The value of the transmission rate of *B. pertussis*, β, is derived from the basic reproduction number R_0, which can be estimated using empirical estimates of the average age at first infection A and the mean life-span L. Anderson and May (1991) proposed the approximate relation $R_0 \approx L/A$ (assuming age-independent mortality), which lead them to an estimated value of around 17 for whooping cough in pre-vaccine era England and Wales as well as the USA. However, that formula needs to be amended when waning of immunity is taken into account (Wearing and Rohani, unpublished manuscript). In our model, the basic reproduction number of *B. pertussis* can be expressed as an approximate function of the average age at first infection A and the rate of waning immunity σ (see

Appendix for an exact expression):

$$R_0 \approx \frac{(1/A)+\sigma}{\mu+\sigma} \tag{2}$$

Using $1/\mu = 70$ years, $A = 4{\cdot}5$ years (Anderson and May, 1982) and $1/\sigma = 50$ years, we get $R_0 \approx 7$ for *B. pertussis*. The transmission rate β is then given by $R_0\ (\mu+\gamma)$ and the basic reproduction number of *B. parapertussis* by $R_0\,\varphi$. The numerical values of parameters φ, θ_p, θ_{pp} and θ_v, which are specific to this model and for which no empirical estimate is available, were varied extensively between 0 and 1. We also explored the effects of wide variations in immune period $1/\sigma$ and vaccine coverage v. Although not shown here, we checked that the patterns presented in this paper were not affected qualitatively by variations in other parameters (A, μ or γ).

RESULTS

Persistence of pertussis and parapertussis

The system has four possible equilibrium points: no pathogen, *B. pertussis* alone, *B. parapertussis* alone and both pathogens present. Only the first two can be expressed analytically. To determine their stability, we assessed the ability of each pathogen to invade equilibria from which it is absent. Further details about the following expressions are given in the Appendix.

In the absence of *B. parapertussis*, elimination of *B. pertussis* by vaccination is feasible if immunity lasts long enough. The critical vaccine coverage, above which *B. pertussis* cannot persist, is given by

$$v_p^c = (1-1/R_0)(1+\sigma/\mu) \tag{3}$$

which only holds if the right-hand term is equal to or less than one. Using equation (2), this condition can be re-written as: $\sigma \leqslant (A\mu^2)/(1-2A\mu)$ Using the exact expression for R_0 derived in the Appendix instead of equation (2) leads to a more complicated expression but we checked that the numerical values were very close. Numerically, with $A = 4{\cdot}5$ years and $1/\mu = 70$ years, our model predicts that *B. pertussis* cannot be controlled by single dose vaccination if the average duration of immunity $1/\sigma$ is shorter than 948 years. In the following, we will assume that this is the case, so that *B. pertussis* remains endemic with any level of vaccine coverage in the absence of *B. parapertussis*. Note that the feasibility of *B. pertussis* control would be further reduced if we considered limited efficacy of the vaccine, i.e. partial susceptibility to *B. pertussis* despite immunization. On the other hand, such pessimistic estimates are in part caused by the simplistic structure of the model: factors such as spatial structure, age structure or stochasticity would probably make vaccination more likely to control infection, but we leave those considerations for further studies. Nevertheless, our results highlight the proposition that more consideration should be given to protocols of booster vaccination if eradication is to be successful.

In the absence of *B. pertussis*, *B. parapertussis* can theoretically be controlled through anti-pertussis vaccination, depending on the balance between vaccine efficacy against *B. parapertussis* θ_v and *B. parapertussis* relative fitness φ. The critical vaccine coverage is given by:

$$v_{pp}^c = \frac{1}{\theta_v}\left(1-\frac{1}{R_0\varphi}\right)(1+\sigma/\mu) \tag{4}$$

which can only be achieved if the right-hand term is equal to or less than one, i.e.

$$R_0\varphi \leqslant \frac{\mu+\sigma}{\mu(1-\theta_v)+\sigma}. \tag{5}$$

When *B. pertussis* is endemic, *B. parapertussis* can spread and persist in the population if:

$$R_0\varphi > \frac{1}{1+\theta_p(1/R_0-1)+\frac{\mu}{\sigma+\mu}\left[1-v(\theta_v-\theta_p)\right]}. \tag{6}$$

The dependence on v of the right-hand expression shows that anti-pertussis vaccination can hinder the spread of *B. parapertussis* only if the vaccine confers more cross-protection than natural infection with *B. pertussis* ($\theta_v > \theta_p$).

When *B. parapertussis* is endemic, the condition for *B. pertussis* invasion cannot be expressed algebraically. Numerical analysis shows that, with high enough values of φ (i.e. the fitness of *B. parapertussis* being comparable to *B. pertussis*), *B. parapertussis* can stop *B. pertussis* from invading in the presence of anti-pertussis vaccination (Fig. 2).

Coexistence is possible when both pathogens can invade each other's endemic equilibrium. This can be checked numerically by calculating the eigenvalues of the jacobian matrix of system (1).

Fig. 2 illustrates the effects of the key parameters of the model on the persistence of the two pathogens. There are wide areas of realistic parameter values that allow for the coexistence of *B. pertussis* and *B. parapertussis*. One of the main predictions is that, in the presence of anti-pertussis vaccination, the advantage to *B. parapertussis* conferred by immune evasion must be balanced by a fitness cost (modelled here as lower infectivity) – otherwise *B. pertussis* would be eliminated in the face of the asymmetric immunity. The only condition that allows coexistence without such a cost to *B. parapertussis* is a combination of low anti-pertussis vaccine coverage and short-lasting immunity. Surprisingly, the scope of *B. parapertussis* immune evasion (measured by θ_p and θ_v compared to θ_{pp}) has limited impact on coexistence. These parameters affect only the *relative* fitness of each pathogen, which depends on the

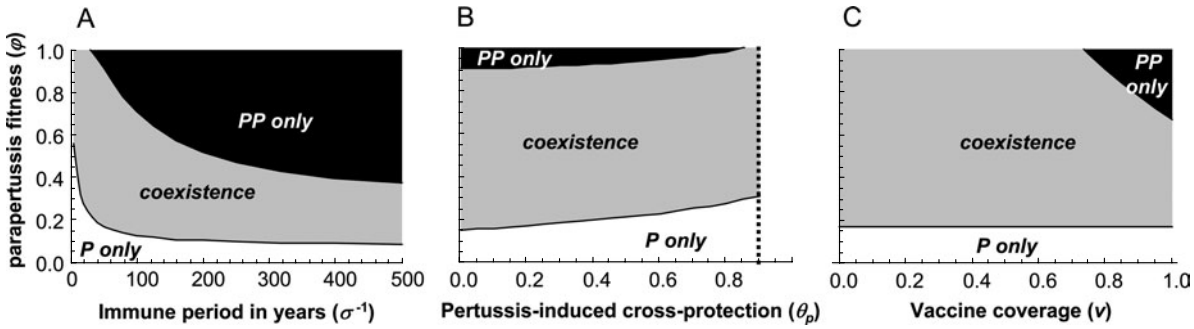

Fig. 2. Stable equilibria (*B. pertussis* [P] only, *B. parapertussis* [PP] only, or coexistence) for different ranges of parameter values (see axes legends). Default values for the three panels: lifespan $1/\mu = 70$ years, infectious period $1/\gamma = 21$ days, immune period $1/\sigma = 50$ years, $R_0 = (1/4{\cdot}5 + \sigma)/(\mu + \sigma) \approx 7{\cdot}1$ with default values (but note that R_0 varies with σ in panel A), vaccine coverage $v = 0{\cdot}8$, *B. pertussis*-induced cross-protection $\theta_p = \theta_v = 0{\cdot}2$, *B. parapertussis*-induced cross-protection $\theta_{pp} = 0{\cdot}9$.

prevalence of its competitor. As we will show next, the effect of cross-immunity parameters is most visible on relative prevalences. We emphasize the fact that the criterion for persistence considered here is based on a deterministic model with an infinite population size. In a stochastic model with a finite population size, persistence would critically depend on variations in prevalence.

Relative prevalence

Under the scenario of stable coexistence of *B. pertussis* and *B. parapertussis*, we estimated their relative prevalences at the endemic equilibrium and assessed the effect of anti-pertussis vaccination. Broadly speaking, increasing the vaccine coverage reduces *B. pertussis* but not *B. parapertussis* prevalence, thus giving the latter a relative competitive advantage (Fig. 3A). We then investigated in more detail how vaccination affects the absolute and relative incidence of *B. parapertussis*. A key factor is the cross-protection conferred by vaccination θ_v compared to that conferred by primary infection with *B. pertussis* θ_p. Only if the two parameters are significantly different can vaccination modify the absolute prevalence of *B. parapertussis* (Fig. 3B). As mentioned in the introduction, the relative prevalence of *B. pertussis* and *B. parapertussis* has been the subject of much debate, notably because of differences in rates of reporting. As illustrated on Fig. 3A, it is possible to estimate, for a given set of parameter values, a theoretical vaccine coverage v_{eq} that results in equal prevalences of the two infections. The sensitivity of that threshold to *B. parapertussis* parameters is shown on Fig. 3C and 3D. The relative fitness of *B. parapertussis* and its ability to evade *B. pertussis*-specific immunity are naturally very important factors determining the ratio of *B. pertussis* to *B. parapertussis*. Typically, a fitness cost for *B. parapertussis* of at least 40% (i.e. $\varphi < 0{\cdot}6$) is needed to allow the dominance of *B. pertussis*. Interestingly, if infection-induced cross-immunity θ_p is fixed, the threshold vaccine coverage v_{eq} (above which *B. parapertussis* dominates) is relatively insensitive to vaccine induced cross-protection θ_v. In other words, for a given vaccine coverage, the ratio of *B. pertussis* to *B. parapertussis* incidence would not be much affected by a drop in vaccine efficacy against *B. parapertussis*.

Endemic dynamics

Although the study of equilibrium states can help predict the long-term effects of changes in vaccine coverage or efficacy, they ignore transient dynamics of potentially great importance (Rohani, Keeling and Grenfell, 2002; Restif and Grenfell, 2007). We performed numerical integration of system (1) using various sets of parameter values (Fig. 4). Simulations were started at the coexistence endemic equilibrium in the absence of vaccine, and vaccine coverage was increased linearly over 20 years up to a given value. In the years that follow the initiation of the vaccination campaign, *B. pertussis* tends to exhibit a pattern previously described as the 'honeymoon period' (McLean, 1995): prevalence drops to low levels, followed by a series of small outbreaks which converge towards a steady state. This pattern is amplified by the presence of *B. parapertussis*, but is attenuated if immunity is not life-long (Fig. 4). The increase in *B. pertussis* prevalence after stabilisation of vaccine coverage can be understood by tracking the dynamics of the whole system. Following the drop in *B. pertussis* prevalence caused by vaccination, the number of individuals immune to *B. parapertussis* only (R_{pp}) increases and eventually boosts the number of secondary infections with *B. pertussis* (Fig. 5). The increase is therefore weaker when immunity is shorter-lived, as this depletes the pool of individuals susceptible to *B. pertussis* only (R_{pp}).

In contrast, *B. parapertussis* shows only small perturbations during the same period. As documented by Lautrop (1971), the oscillations of the two

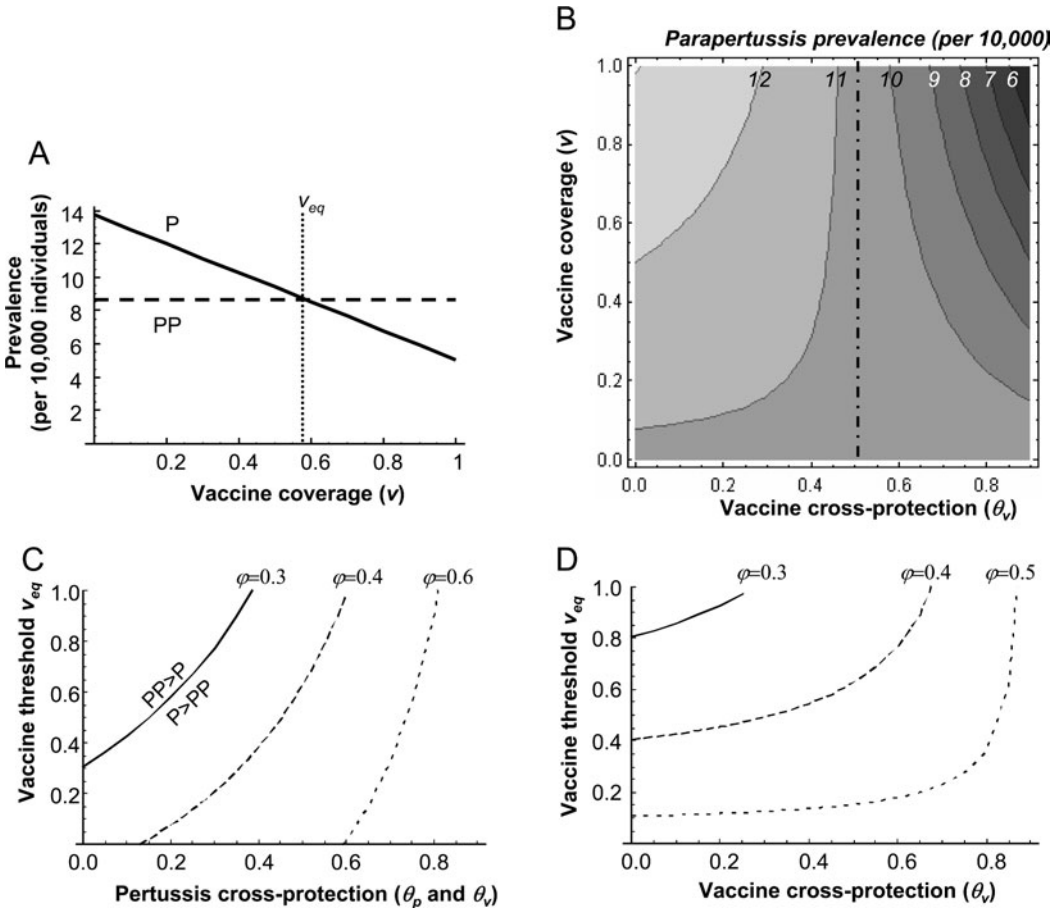

Fig. 3. (A) Prevalence at steady state of *B. pertussis* (solid line) and *B. parapertussis* (dashed line) against vaccine coverage; the vertical dotted line shows the position of v_{eq}, the vaccine coverage that results in equal prevalences of the two pathogens (numerical values as in Figure 2, and $\varphi = 0{\cdot}3$). (B) *B. parapertussis* prevalence at steady state (shades of grey; numbers on isoclines are prevalence per 10 000) against vaccine cross-protection θ_v (horizontal scale) and vaccine coverage v (vertical scale); the vertical dashed line shows the position of θ_p (numerical values as in Fig. 2, except $\theta_p = 0{\cdot}5$). (C) Vaccine threshold v_{eq} (above which *B. parapertussis* prevalence is higher than that of *B. pertussis*) against *B. pertussis*-induced cross-protection $\theta_p = \theta_v$ for different values of *B. parapertussis* fitness φ. (D) As in (C), except that θ_p is set to 0·5.

pathogens are out of phase (i.e. *B. parapertussis* peaks coincide with *B. pertussis* troughs). Only if vaccine-induced cross-protection is weaker than the protection caused by *B. pertussis* infection (i.e. $\theta_v < \theta_p$), do we predict higher peaks of *B. parapertussis* when vaccine coverage reaches its plateau (year 20 on Fig. 4C). However, the perturbations of *B. parapertussis* dynamics do not mirror those of *B. pertussis* unless we assume symmetric cross-protection from infection ($\theta_p = \theta_{pp}$) and weaker vaccine cross-protection ($\theta_v < \theta_p$) (Fig. 4D).

DISCUSSION

In this paper we have investigated the coexistence of two related pathogens in a host population. Because of cross-immunity, they are in competition for access to hosts and they use different strategies to cope: evade cross-immunity (and gain access to a wider pool of hosts) or invest in higher infectivity (and cause more cases among naïve hosts). We used fresh experimental results to apply this model to the dynamics of *Bordetella pertussis* and *B. parapertussis*. Beyond this specific example, our work highlights promising trends in the field of infectious diseases dynamics of co-circulating strains.

Parapertussis dynamics

The basis for this study was the recent finding that *B. parapertussis* can colonise mice immunized against *B. pertussis*, whereas immunisation with *B. parapertussis* is protective against both pathogens (Wolfe *et al.* 2007). This was unexpected as it implies a strong competitive advantage to *B. parapertussis*, at odds with the general view that *B. pertussis* is much more prevalent than its relative in human populations. We therefore explored the additional assumption that *B. parapertussis* may pay a cost, through reduced infectivity. Given the lack of conclusive data on the relative fitness of the two pathogens, we allowed for extensive variations in the cost

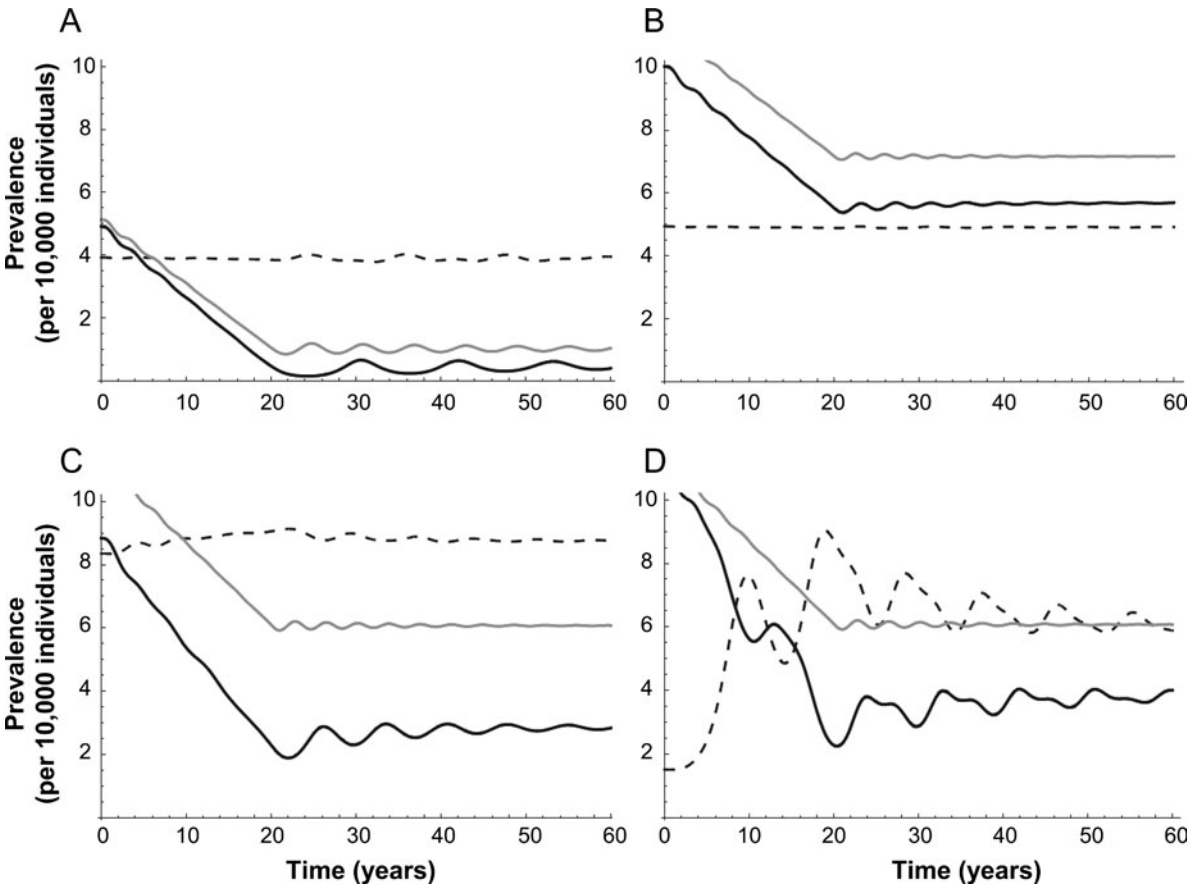

Fig. 4. Dynamics of *B. pertussis* (solid black line) and *B. parapertussis* prevalence (black dashed line), plotted together with *B. pertussis* prevalence (grey line) in the absence of *B. parapertussis*. Initially, the system is at equilibrium without vaccination. Vaccine coverage increases linearly from $v=0$ at time 0 to $v=0{\cdot}75$ (panels A and B) or to $v=0{\cdot}95$ (panels C and D) at time 20 years; then v remains constant. Numerical values: $1/\mu=70$ years, $1/\gamma=21$ days, $\theta_{pp}=0{\cdot}8$, $R_0=(1/4{\cdot}5+\sigma)/(\mu+\sigma)$ (so $R_0\approx 15{\cdot}6$ in panel A and 7·1 elsewhere); (A) $\sigma=0$, $\varphi=0{\cdot}3$, $\theta_p=\theta_v=0{\cdot}3$; (B) $\sigma=0{\cdot}02$ years^{-1}, $\varphi=0{\cdot}3$, $\theta_p=\theta_v=0{\cdot}3$; (C) $\sigma=0{\cdot}02$ years^{-1}, $\varphi=0{\cdot}5$, $\theta_p=0{\cdot}3$, $\theta_v=0{\cdot}1$; (D) $\sigma=0{\cdot}02$ years^{-1}, $\varphi=0{\cdot}5$, $\theta_p=0{\cdot}8$, $\theta_v=0{\cdot}3$.

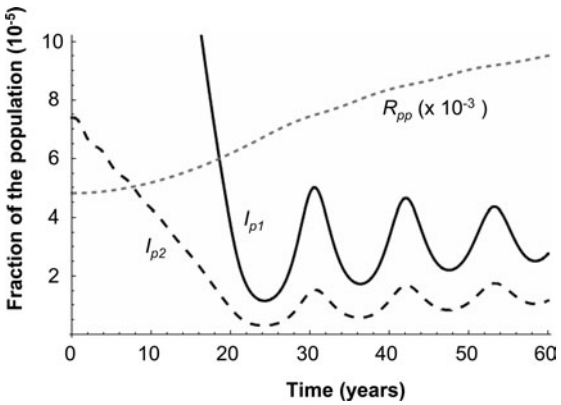

Fig. 5. Dynamics of primary cases of *B. pertussis* I_{p1} (black solid line), secondary cases of *B. pertussis* I_{p2} (dashed black line) and individuals immune to *B. parapertussis* only after primary infection R_{pp} (dotted grey line). Same conditions as in Fig. 4A.

paid by *B. parapertussis*. Depending on the trade-off between fitness and immune evasion, our model predicts the conditions for coexistence. As illustrated on Fig. 2, we found that *B. parapertussis* relative fitness (φ) was one of the main determinants of coexistence. Cross-protection parameters had limited effects on the ability of either pathogen to invade but had substantial effects on relative prevalence (Figs 3 and 4). Such variations in prevalence can actually make the difference between persistence and extinction in a population with finite size. Although detailed quantitative investigations are beyond the scope of this study, we expect the precise effects of asymmetric cross-protection on pertussis and parapertussis dynamics to vary locally with population size and structure. Regarding our assumption of fitness reduction, it is of course possible to imagine other possible sources of competitive advantage for *B. pertussis*, such as preferential access to certain categories of hosts (based on age or immunocompetence for example) or spatial spread (based on differential persistence in given environments for example); but these assumptions remain speculative in the absence of any empirical support.

Anti-pertussis vaccination gives a further advantage to *B. parapertussis* because of weak cross-protection. Our main conclusion regarding

immunisation is that, because of the asymmetry in cross-immunity, the introduction of anti-pertussis vaccination should have little effect on the absolute prevalence of *B. parapertussis*, while that of *B. pertussis* should drop. Should the vaccine be more or less cross-protective than *B. pertussis* infection, then the prevalence of *B. parapertussis* would slightly decrease or increase. But unless we ignore asymmetric cross-immunity (Fig. 4D), we do not expect a major rise of *B. parapertussis* following anti-pertussis vaccination. Despite the limited information available on *B. parapertussis* incidence, two studies appear to corroborate our qualitative insights. First, Lautrop (1971) reported a decrease in the incidences of both *B. pertussis* and *B. parapertussis* in the ten years that followed the start of mass vaccination in 1959 in Denmark. Interestingly, because he expected the vaccine to confer no cross-protection, he stated that ''the reduced size of the *B. parapertussis* peaks after 1958–59 poses a problem.'' More recently, following the reintroduction of anti-pertussis vaccination in Germany in 1994, Liese *et al.* (2003) observed a drop in *B. pertussis* incidence (from 21·7 per 1000 person-years during 1993–95 to 4·8 per 1000 person-years during 1997–99) together with a slight increase in *B. parapertussis* (from 1·6 per 1000 person-years in 1993–95 to 2·8 per 1000 person-years in 1997–99). Although the latter two studies are difficult to compare due to the different methods used, the contrasted trends in *B. parapertussis* incidence in the two countries might have been caused by differences in cross-protection conferred by whole cell *B. pertussis* (in the Danish study) and acellular vaccine (in the German study). However, it is also conceivable that the drop in Danish *B. parapertussis* could be coincident due to concurrent secular decreases in birth rates, as discussed for measles by Earn *et al.* (2000). Clearly, more longitudinal surveys would be needed to assess the actual incidence of *B. parapertussis* and its response to vaccination.

Asymmetric cross-immunity

Cross-immunity between strains of pathogens has received particular attention in the context of vaccine development. Indeed, the emergence of antigenic variants that can infect immunized hosts threatens the efficacy of existing vaccines – e.g. human influenza A (Ferguson *et al.* 2003) or equine influenza (Grenfell *et al.* 2004) – as well as the development of new ones – e.g. HIV (McMichael, Mwau and Hanke, 2002) or malaria (Genton *et al.* 2002). These concerns have motivated a growing literature on mathematical models for antigenically diverse pathogens in the presence of a vaccine (McLean, 1995; Gupta, Ferguson and Anderson, 1997; Lipsitch, 1997; White *et al.* 1998; Wilson, Nokes and Carman, 1999; Park *et al.* 2004; Zhang, Auranen and Eichner, 2004; Elbasha and Galvani, 2005; Gandon and Day, 2007; Restif and Grenfell, 2007). In all of these studies, the main argument is the emergence of a variant strain favoured by a vaccine targeting specifically an endemic strain, because of imperfect cross-immunity. Although we used a different framework in which the two pathogens coexist before the vaccine is introduced, the mechanisms at stake are the same. In some cases, the variant strain has a lower fitness than the resident strain, so that it can only spread if vaccine specificity outweighs this cost. With the exception of White *et al.* (1998), who briefly mention this scenario, asymmetric cross-immunity in the absence of vaccine has not been considered (see Lipsitch *et al.* 2000 for asymmetric interactions between *Streptococcus pneumoniae* strains in the presence of vaccination). The reasons for this lack of interest are twofold. First, conceptually, asymmetric cross-immunity as considered in this study gives a further advantage to the strain not targeted by the vaccine – combining two benefits may not appeal to modellers unless they have a good reason to do so. This leads to the second reason: the lack of empirical evidence. As far as we know, the *Bordetella* case is a first. It will be interesting to learn if it is an exception, or whether, perhaps, the absence of other cases is due to a lack of investigation.

A recent analytical tool for multi-strain pathogens – antigenic cartography – may provide broader insights into the generality of asymmetric cross-immunity (Smith *et al.* 2004). Based on haemagglutination assay tables, this technique provides a graphical representation of virus isolates and immune sera in the 'antigenic space'. The distance between a strain and a serum in that space indicates the ability of antibodies to bind virus particles. It is then possible to deduce an 'antigenic distance' between two viral strains based on their respective distances to a given set of sera. Conceptually, this is similar to the antigenic spaces used in mathematical models for multiple strain dynamics (e.g. Gog and Swinton, 2002; Gomes, Medley and Nokes, 2002), except for their lack of explicit consideration of serology. If cross-immunity between two strains is described by a distance between these two strains, then symmetry is essentially assumed. However, if cross-immunity is described, more accurately, as the cross-reaction between strains and sera, then the significance of any asymmetries can be fully explored. The antigenic map of human influenza A produced by Smith *et al.* (2004) in Fig. S3, which shows the respective locations of virus strains and their immune sera, suggests that asymmetric cross-immunity is common. Including empirical antigenic spaces in mathematical models would certainly be challenging but it may lead to a better understanding of multiple strain dynamics.

Combining models

More generally, this study illustrates the strength of multi-disciplinary approaches in the field of infectious diseases. Although epidemiological surveys are still needed to gain a full understanding of the spread of infection in natural populations, the combination of experimental and mathematical models is a quick and cost-effective tool to explore hypotheses and make specific predictions. Mathematical models inspired by experiments have flourished in life sciences over the last three decades, boosted by the advent of personal computers allowing numerical analysis and simulations of increasingly complex systems, and by a growing interest among mathematicians and physicists. However, those theoretical models are still quite often met with distrust from biologists, on the grounds of being too simplistic or relying on unproven hypotheses: see for example Smith's (2002) comment on Gandon *et al.*'s (2001), or Kitching *et al.*'s (2007) criticism of Tildesley *et al.* (2006). In this context, it is important to acknowledge that models, be they *in silico*, *in vitro* or *in vivo*, are only intended to help understand specific aspects of complex systems, and therefore the predictions they produce are always uncertain to some extent. The way forward is then to set up a dialogue between these different approaches, through which theoretical predictions can be tested in the lab and experimental results can help refine mathematical models.

In this paper, we have extrapolated the results of experiments on individual mice, to predict epidemiological consequences at the level of human populations. In building the model, we had to decide how measured reductions in bacterial colonisation should be translated in terms of susceptibility and infectiousness of individuals in a population. We explored one possible scenario which offers the advantage of an easy and flexible integration into well-studied mathematical frameworks. Further experimental work will obviously be needed to reconcile within- and between-host dynamics. Neither the murine model nor the simple theoretical framework used here can faithfully reproduce the complex mechanisms of *B. pertussis* and *B. parapertussis* infection dynamics in a real population. As suggested by the scarce data published on *B. parapertussis*, a detailed survey of the actual epidemiology of the pathogen would be difficult and expensive – though, we believe, very important to attempt. In contrast, our models effectively provide a first series of indications on some of the processes at stake, and offer new keys to interpret empirical observations. We are confident that further research initiated by this work will enable us to improve our models and make more accurate predictions on the circulation of these pathogens.

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APPENDIX

Mean age at first infection in a model with waning immunity

We consider a simple extension of the SIR model with a fourth compartment S_w for people becoming susceptible after losing their immunity. At steady state, the age structure in the population is described by the following system of equations (based on Anderson and May, 1991):

$$\begin{cases} dS/da = -(\Lambda+\mu)S \\ dI/da = \Lambda(S+S_w)-(\mu+\gamma)I \\ dR/da = \gamma I-(\mu+\sigma)R \\ dS_w/da = \sigma R-(\Lambda+\mu)S_w \end{cases}$$

where a represents age as a continuous variable, $\Lambda = \int_0^\infty \beta I(a)da$ is the force of infection and the other parameters (which we assume to be age-independent) are as defined in Table 1. The age-distribution of naïve individuals therefore follows: $S(a) = \exp[-(\Lambda+\mu)a]$. Following Anderson and May (1991), we then express the mean age at first expression A as the first moment of the $\Lambda S(a)$ distribution:

$$A = \frac{\int_0^\infty a\Lambda S(a)da}{\int_0^\infty \Lambda S(a)da} = \frac{1}{\Lambda+\mu}$$

Relation between R_0 and mean age at first infection

In our model the basic reproduction number is given by $R_0 = \beta/(\mu+\gamma)$, while the mean age at first infection in a model with age-independent death rate is given by

$$A = \frac{1}{\beta I^* + \mu}$$

where I^* is the proportion infected at the endemic equilibrium:

$$I^* = \frac{\mu+\sigma}{\gamma+\mu+\sigma}\left(1-\frac{1}{R_0}\right).$$

We combined those three equations to obtain, after some algebra:

$$R_0 = \frac{A\gamma\sigma+\gamma+\mu+\sigma}{A(\gamma+\mu)(\mu+\sigma)}$$

For pertussis $\gamma >> (\mu,\ \sigma, 1/A)$, hence, by rewriting:

$$R_0 = \frac{1/A+\sigma}{(\mu+\sigma)(1+\mu/\gamma)} + \frac{1}{A\gamma(1+\mu/\gamma)},$$

we finally obtain:

$$R_0 \approx \frac{1/A+\sigma}{\mu+\sigma}.$$

Vaccine thresholds

The critical vaccine coverage is defined for each disease as the minimum coverage preventing the invasion or persistence of infection. Its expression can be obtained either by setting the steady state fraction of infected individuals (endemic equilibrium) to zero or by setting the invasion rate of infection from the disease-free steady state to zero, and solving for the vaccine coverage v. Both methods are equivalent and we shall use the latter.

For pertussis alone, the rate of invasion from disease-free state $(\hat{S},\ \hat{V})$ is given by:

$$\frac{1}{\Lambda_p}\frac{d\Lambda_p}{dt} = \hat{S} - \frac{1}{R_0} = 1 - v\frac{\mu}{\mu+\sigma} - \frac{1}{R_0}.$$

Hence the corresponding critical vaccine coverage:

$$v_p^c = (1-1/R_0)(1+\sigma/\mu).$$

For parapertussis alone, the rate of invasion from disease-free state $(\hat{S},\ \hat{V})$ is given by:

$$\begin{aligned}\frac{1}{\Lambda_{pp}}\frac{d\Lambda_{pp}}{dt} &= \varphi\hat{S} + \varphi(1-\theta_v)\hat{V} - \frac{1}{R_0}\\ &= \varphi\left(1 - v\frac{\mu}{\mu+\sigma}\right) + \varphi(1-\theta_v)\\ &\quad \times v\frac{\mu}{\mu+\sigma} - \frac{1}{\mathbf{R_0}}\end{aligned}$$

Hence the corresponding critical vaccine coverage:

$$v_{pp}^c = \frac{1}{\theta_v}\left(1 - \frac{1}{R_0\varphi}\right)(1+\sigma/\mu).$$

Last, the vaccine threshold that prevents the spread of parapertussis in the presence of pertussis is obtained by setting to zero the following invasion rate of parapertussis from the pertussis-endemic steady state $(S^*,\ V^*,\ I_p^*,\ R_p^*)$:

$$\begin{aligned}\frac{1}{\Lambda_{pp}}\frac{d\Lambda_{pp}}{dt} &= \varphi S^* + \varphi(1-\theta_v)V^*\\ &\quad + \varphi(1-\theta_{pp})(I_p^* + R_p^*) - \frac{1}{R_0}\\ &= \frac{\varphi}{R_0} + \varphi(1-\theta_v)v\frac{\mu}{\mu+\sigma} + \varphi(1-\theta_{pp})\\ &\quad \times \left[1 - \frac{1}{R_0} - v\frac{\mu}{\mu+\sigma}\right] - \frac{1}{R_0}\end{aligned}$$

which leads to the following threshold:

$$v_{pp}^p = \frac{1}{\theta_v - \theta_p}\left(1 - \theta_p - \frac{1-\varphi\theta_p}{R_0\varphi}\right)(1+\sigma/\mu).$$

The condition $v > v_{pp}^p$ can also be written in terms of *B. parapertussis* fitness as:

$$R_0\varphi > \frac{1}{1+\theta_p(1/R_0-1) + \frac{\mu}{\sigma+\mu}\left[1 - v(\theta_v - \theta_p)\right]}$$

REFERENCES

Anderson, R. M. and May, R. M. (1982). Directly transmitted infectious diseases: control by vaccination. *Science* **215**, 1053–1061.

Anderson, R. M. and May, R. M. (1991). *Infectious Diseases of Humans*, Oxford University Press, Oxford.

Bergfors, E., Trollfors, B., Taranger, J., Lagergard, T., Sundh, V. and Zackrisson, G. (1999). Parapertussis and pertussis: differences and similarities in incidence, clinical course, and antibody responses. *International Journal of Infectious Diseases* **3**, 140–146.

Broutin, H., Rohani, P., Guégan, J.-F., Grenfell, B. T. and Simondon, F. (2004). Loss of immunity to pertussis in a rural community in Senegal. *Vaccine* **22**, 594–596.

Centers for Disease Control and Prevention (2007). Nationally notifiable infectious diseases, United States 2007, revised. Centers for Disease Control and Prevention, Atlanta.

Cimolai, N. and Trombley, C. (2001). Molecular diagnostics confirm the paucity of parapertussis activity. *European Journal of Pediatrics* **160**, 518–525.

Diavatopoulos, D. A., Cummings, C. A., Schouls, L. M., Brinig, M. M., Relman, D. A. and Mooi, F. R. (2005). *Bordetella pertussis*, the causative agent of whooping cough, evolved from a distinct, human-associated lineage of *B. bronchiseptica*. *Public Library of Science Pathogens* **1**, 45–55.

Dragsted, D. M., Dohn, B., Madsen, J. and Jensen, J. S. (2004). Comparison of culture and PCR for detection of *Bordetella pertussis* and *Bordetella parapertussis* under routine laboratory conditions. *Journal of Medical Microbiology* **53**, 749–754.

Earn, D. J. D., Rohani, P., Bolker, B. and Grenfell, B. T. (2000). A simple model for complex dynamical transitions in epidemics. *Science* **287**, 667–670.

Elbasha, E. H. and Galvani, A. P. (2005). Vaccination against multiple HPV types. *Mathematical Biosciences* **197**, 88–117.

Eldering, G. and Kendrick, P. (1938). *Bacillus parapertussis*: a species resembling both *Bacillus pertussis* and *Bacillus bronchisepticus* but identical with neither. *Journal of Bacteriology* **35**, 561–572.

Eldering, G. and Kendrick, P. (1952). Incidence of parapertussis in the Grand Rapids Area as indicated by 16 years' experience with diagnostic cultures. *American Journal of Public Health and the Nation's Health* **42**, 27–31.

Ferguson, N. M., Galvani, A. P. and Bush, R. M. (2003). Ecological and immunological determinants of influenza evolution. *Nature* **422**, 428–433.

Frank, S. A. and Barbour, A. G. (2006). Within-host dynamics of antigenic variation. *Infection, Genetics and Evolution* **6**, 141–146.

Frühwirth, M., Neher, C., Schmidt-Schläpfer, G. and Allerberger, F. (2002). *Bordetella pertussis* and *Bordetella parapertussis* infection in an Austrian pediatric outpatient clinic. *Wiener klinische Wochenschrift* **114**, 377–382.

Gandon, S. and Day, T. (2007). The evolutionary epidemiology of vaccination. *Journal of the Royal Society Interface* **4**, 803–817.

Gandon, S., Mackinnon, M. J., Nee, S. and Read, A. F. (2001). Imperfect vaccines and the evolution of pathogen virulence. *Nature* **414**, 751–756.

Genton, B., Betuela, I., Felger, I., Al-Yaman, F., Anders, R. F., Saul, A., Rare, L., Baisor, M., Lorry, K., Brown, G. V., Pye, D., Irving, D. O., Smith, T. A., Beck, H.-P. and Alpers, M. P. (2002). A recombinant blood-stage malaria vaccine reduces *Plasmodium falciparum* density and exerts selective pressure on parasite populations in a phase 1–2b trial in Papua New Guinea. *Journal of Infectious Diseases* **185**, 820–827.

Gog, J. and Grenfell, B. T. (2002). Dynamics and selection of many-strain pathogens. *Proceedings of the National Academy of Sciences, USA* **99**, 17209–17214.

Gog, J. and Swinton, J. (2002). A status-based approach to multiple strain dynamics. *Journal of Mathematical Biology* **44**, 169–184.

Gomes, M. G. M., Medley, G. F. and Nokes, D. J. (2002). On the determinants of population structure in antigenically diverse pathogens. *Proceedings of the Royal Society of London, Series B* **269**, 227–233.

Granström, M. and Askelöf, P. (1982). Parapertussis: an abortive pertussis infection? *The Lancet* **320**, 1233–1290.

Grenfell, B. T., Pybus, O. G., Gog, J. R., Wood, J. L. N., Daly, J. M., Mumford, J. A. and Holmes, E. C. (2004). Unifying the epidemiological and evolutionary dynamics of pathogens. *Science* **303**, 327–332.

Gupta, S., Ferguson, N. M. and Anderson, R. M. (1997). Vaccination and the population structure of antigenically diverse pathogens that exchange genetic material. *Proceedings of the Royal Society of London, Series B* **264**, 1435–1443.

He, Q., Arvilommi, H., Viljanen, M. K. and Mertsola, J. (1999). Outcomes of *Bordetella* infection in vaccinated children: effects of bacterial number in the nasopharynx and patient age. *Clinical and Diagnostic Laboratory Immunology* **6**, 534–536.

He, Q., Viljanen, M. K., Arvilommi, H., Aittanen, B. and Mertsola, J. (1998). Whooping cough caused by *Bordetella pertussis* and *Bordetella parapertussis* in an immunized population. *Journal of the American Medical Association* **260**, 635–637.

Kamo, M. and Sasaki, A. (2002). The effects of cross-immunity and seasonal forcing in a multi-strain epidemic model. *Physica D* **165**, 228–241.

Khelef, N., Danve, B., Quentin-Millet, M.-J. and Guiso, N. (1993). *Bordetella pertussis* and *Bordetella parapertussis*: two immunologically distinct species. *Infection and Immunity* **61**, 486–490.

Kitching, R. P., Taylor, N. M. and Thrusfield, M. V. (2007). Vaccination strategies for foot-and-mouth disease. *Nature* **445**, E12.

Koelle, K., Cobey, S., Grenfell, B. T. and Pascual, M. (2006). Epochal evolution shapes the phylodynamics of interpandemic influenza A (H3N2) in humans. *Science* **314**, 1898–1903.

Lautrop, H. (1958). Observations on parapertussis in Denmark. *Acta Pathologica et Microbiologica Scandinavica* **43**, 255–266.

Lautrop, H. (1971). Epidemics of parapertussis – 20 years' observations in Denmark. *The Lancet* **297**, 1195–1198.

Letowska, I. and Hryniewicz, W. (2004). Epidemiology and characterization of *Bordetella parapertussis* strains isolated between 1995 and 2002 in and around Warsaw, Poland. *European Journal of Clinical Microbiology and Infectious Diseases* **23**, 499–501.

Liese, J. G., Renner, C., Stojanov, S., Belohradsky, B. H. and The Munich Vaccine Study Group (2003). Clinical and epidemiological picture of *B. pertussis* and *B. parapertussis* infections after introduction of acellular pertussis vaccines. *Archives of Disease in Childhood* **88**, 684–687.

Lipsitch, M. (1997). Vaccination against colonizing bacteria with multiple serotypes. *Proceedings of the National Academy of Sciences, USA* **94**, 6571–6576.

Lipsitch, M., Dykes, J. K., Johnson, S. E., Ades, E. W., King, J., Briles, D. E. and Carlone, G. M. (2000). Competition among *Streptococcus pneumoniae* for intranasal colonization in a mouse model. *Vaccine* **18**, 2895–2901.

Mastrantonio, P., Stefanelli, P., Giuliano, M., Herrera Rojas, Y., Ciofi Degli Atti, M. L., Anemona, A. and Tozzi, A. E. (1998). *Bordetella parapertussis* infection in children: epidemiology, clinical symptoms, and molecular characteristics of isolates. *Journal of Clinical Microbiology* **36**, 999–1002.

Mattoo, S. and Cherry, J. D. (2005). Molecular pathogenesis, epidemiology, and clinical manifestations of respiratory infections due to *Bordetella pertussis* and other *Bordetella* subspecies. *Clinical Microbiology Reviews* **18**, 326–382.

Mclean, A. R. (1995). Vaccination, evolution and changes in the efficacy of vaccines: a theoretical framework. *Proceedings of the Royal Society of London, Series B* **261**, 389–393.

McMichael, A., Mwau, M. and Hanke, T. (2002). HIV T cell vaccines, the importance of clades. *Vaccine* **20**, 1918–1921.

Musser, J. M., Hewlett, E. L., Peppler, M. S. and Selander, R. K. (1986). Genetic diversity and relationships in populations of *Bordetella* spp. *Journal of Bacteriology* **166**, 230–237.

Olin, P., Gustafsson, L., Barreto, L., Hessel, L., Mast, T. C., Van Rie, A., Bogaerts, H. and Storsaeter, J. (2003). Declining pertussis incidence in Sweden following the introduction of acellular pertussis vaccine. *Vaccine* **21**, 2015–2021.

Park, A. W., Wood, J. L. N., Daly, J. M., Newton, J. R., Glass, K., Henley, W., Mumford, J. A. and Grenfell, B. T. (2004). The effects of strain heterology on the epidemiology of equine influenza in a vaccinated

population. *Proceedings of the Royal Society of London, Series B* **271**, 1547–1555.

Redhead, K., Watkins, J., Barnard, A. and Mills, K. H. (1993). Effective immunization against *Bordetella pertussis* respiratory infection in mice is dependent on induction of cell-mediated immunity. *Infection and Immunity* **61**, 3190–3198.

Restif, O. and Grenfell, B. T. (2007). Vaccination and the dynamics of immune evasion. *Journal of the Royal Society Interface* **4**, 143–153.

Rohani, P., Keeling, M. J. and Grenfell, B. T. (2002). The interplay between determinism and stochasticity in childhood diseases. *American Naturalist* **159**, 469–481.

Sato, H. and Sato, Y. (1984). *Bordetella pertussis* infection in mice: correlation of specific antibodies against two antigens, pertussis toxin, and filamentous hemagglutinin with mous protectivity in an intracerebral or aerosol challenge system. *Infection and Immunity* **46**, 415–421.

Sato, Y., Izumiya, K., Sato, H., Cowell, J. L. and Manclark, C. R. (1980). Aerosol infection of mice with *Bordetella pertussis*. *Infection and Immunity* **29**, 261–266.

Smith, D. J., Lapedes, A. S., De Jong, J. C., Bestebroer, T. M., Rimmelzwaan, G. F., Osterhaus, A. D. M. E. and Fouchier, R. A. M. (2004). Mapping the antigenic and genetic evolution of influenza virus. *Science* **305**, 371–376.

Smith, T. (2002). Imperfect vaccines and imperfect models. *Trends in Ecology and Evolution* **17**, 154–156.

Stehr, K., Cherry, J. D., Heininger, U., Schmitt-Grohé, S., Überall, M., Laussucq, S., Eckhardt, T., Meyer, M., Engelhardt, R., Christenson, P. and Group, T. P. V. S. (1998). A comparative efficacy trial in Germany in infants who received either the Lederle/Takeda acellular pertussis component DTP (DTaP) vaccine, the Lederle whole-cell component DTP vaccine, or DT vaccine. *Pediatrics* **101**, 1–12.

Stibitz, S. and Yang, M.-S. (1997). Genomic fluidity of *Bordetella pertussis* assessed by a new method for chromosomal mapping. *Journal of Bacteriology* **179**, 5820–5826.

Tildesley, M. J., Savill, N. J., Shaw, D. J., Deardon, R., Brooks, S. P., Woolhouse, M. E. J., Grenfell, B. T. and Keeling, M. J. (2006). Optimal reactive vaccination strategies for a foot-and-mouth outbreak in the UK. *Nature* **440**, 83–86.

Watanabe, M. and Nagai, M. (2001). Reciprocal protective immunity against *Bordetella pertussis* and *Bordetella parapertussis* in a murine model of respiratory infection. *Infection and Immunity* **69**, 6981–6986.

Wearing, H. J. and Rohani, P. (2006). Ecological and immunological determinants of dengue epidemics. *Proceedings of the National Academy of Sciences, USA* **103**, 11802–11807.

White, L. J., Cox, M. J. and Medley, G. F. (1998). Cross immunity and vaccination against multiple microparasite strains. *IMA Journal of Mathematics Applied in Medicine and Biology* **15**, 211–233.

Willems, R. J. L., Kamerbeek, J., Geuijen, C. A. W., Top, J., Gielen, H., Gaastra, W. and Mooi, F. R. (1998). The efficacy of a whole cell pertussis vaccine and fimbriae against *Bordetella pertussis* and *Bordetella parapertussis* infections in a respiratory mouse model. *Vaccine* **16**, 410–416.

Wilson, J. N., Nokes, D. J. and Carman, W. F. (1999). The predicted pattern of emergence of vaccine-resistant hepatitis B: a cause for concern? *Vaccine* **17**, 973–978.

Wolfe, D. N., Goebel, E. M., Bjørnstad, O. N., Restif, O. and Harvill, E. T. (2007). The O antigen enables *Bordetella parapertussis* to avoid *Bordetella pertussis*-induced immunity. *Infection and Immunity* **75**, 4972–4979.

Wolfram, S. (2007). *The Mathematica Book, 6th Edition*, Wolfram Media.

Zhang, Y., Auranen, K. and Eichner, M. (2004). The influence of competition and vaccination on the coexistence of two pneumococcal serotypes. *Epidemiology and Infection* **132**, 1073–1081.